REMARKS

Claims 12, 14-19 and 39-40 are pending in the instant application. Claims 15-19 have been withdrawn from consideration. The impropriety of the rejection being made final and each new basis for rejection is separately addressed below.

Rejoinder

Applicants respectfully request that Claims 15-19, previously withdrawn as being directed to non-elected species, be rejoined herein. Claims 15-19 depend from and, thus, require all the limitations of Claim 12.

Finality of the rejection

MPEP §706.07(a) provides that "second or any subsequent actions on the merits shall be final, except where the examiner introduces a new ground of rejection that is neither necessitated by applicant's amendment of the claims, nor based on information submitted in an information disclosure statement filed during the period set forth in 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p)." In the present case, neither of these requirements is met.

Claims 12 and 14 were rejected in the first Office Action over Ozaki. The only amendment to claims 12 and 14 were to remove the term "amino linker" from the list of immunostimulatory moieties, since the amino linker claimed by Applicants is actually a 2-aminobutyl-1,3-propanediol. This amendment was not required to overcome the rejection over Ozaki. As Applicants argued in the reply filed May 18, 2009, what Ozaki taught was the replacement of one or more thymidine nucleoside(s) in an oligonucleotide with a uracil nucleoside that has been substituted at the C5 position of the nucleoside base with amino linker arms derived from ethylenediamine (EDA), 1,6-hexanediamine (HMDA) or tris(2-aminoethyl)amine (TAEA). In every case, the nucleoside is still present, but contains one of these base modifications. In contrast, as shown in Figures 9 and 10, Applicants' claimed 2-aminobutyl-1,3-propanediol linker replaces a nucleoside, i.e., there is no nucleoside present at the position of the 2-aminobutyl-1,3-propanediol linker. Thus, the rejection over Ozaki was incorrect from its inception and was properly withdrawn by the Examiner.

The new rejections that have been made are based on references that were not submitted in an information statement. Nor is there any reasonable assertion made as to why Applicants'

minor amendment of claims 12 and 14 necessitated these entirely new rejections over references that first made their appearance in the prosecution of this case in the Final Office Action. Accordingly, Applicants respectfully submit that the finality of the new rejections is improper and request that this finality be withdrawn.

Anticipation Under 35 U.S.C. §102: Cook

Claims 12 is rejected as being anticipated by Cook. Applicants respectfully traverse this rejection. This rejection relies on numerous reversible errors of fact and law, any one of which is fatal to the rejection.

First, the rejection over Cook states that:

> Cook discloses phosphorothioate oligonucleotide sequences joined together by all phosphorothioate linkages (see abstract, SEQ ID NO: 1). The phosphorothioate oligonucleotide CCTTTCGCGACCCACACTA (SEQ ID NO: 1, col. 12, lines 55+) is an immunostimulatory oligonucleotide compound comprising a sequence of formula: 5'-Um……U1-X1-X2-Y-Z-X3-X4-D1……Dm-3' Wherein: Y is a non-natural pyrimidine nucleoside (see underlined C above); Z is a non-natural purine nucleoside (see underlined G above); Wherein the flanking X2 and X3 of CG are immunostimulatory moieties; wherein the immunostimulatory moiety is a 1', 2'-dideoxyribose (see Figure 3 of the instant specification, providing the structure of 1', 2'-dideoxyribose or a phosphorothioate linkage as shown in Figure 1 in the Stein and Cheng reference); and wherein at least one X, U, or D is an immunostimulatory moiety. (OA at pages 2-3).

This mischaracterizes the teaching of Cook in the following multiple ways:

(a) In SEQ ID NO: 1 of Cook, the underlined C is not a non-natural pyrimidine nucleoside; it is cytosine, a natural pyrimidine nucleoside. Note that the key word is "nucleoside", not "nucleotide". To the extent that the PTO is relying on the phosphorothioate linkage as rendering the underlined C "non-natural", it does not, since the term "nucleoside" does not include the phosphorous linkage.

(b) Similarly, in SEQ ID NO: 1 of Cook, the underlined G is not a non-natural purine nucleoside; it is guanosine, a natural purine nucleoside.

(c) There is no 1', 2'-dideoxyribose in SEQ ID NO: 1 of Cook. A 1', 2'-dideoxyribose has no base (it is replaced with a hydrogen), as shown in the instant application in Figure 3.

These are all reversible errors of fact.

Second, the Office Action states that the phosphorothioate of Cook is an immunostimulatory moiety, according to Applicants' definition of immunostimulatory moiety. This impermissibly reads a limitation entirely out of claim 12, which requires that "the immunostimulatory moiety of any of X, U or D is selected from the group consisting of C3-alkyl linker, 2-aminobutyl-1,3-propanediol linker, β-L-deoxynucleoside, 1',2'-dideoxyribose, C3-linker, Spacer 18, 3'-deoxynucleoside, 2'-O-propargyl-ribonucleoside, Spacer 9 and 2'-5' linkage." None of these specific immunostimulatory moieties are taught by Cook. Impermissibly reading out this limitation of claim 12 is a reversible error of law.

For these reasons, Applicants respectfully request that this rejection be withdrawn.

Anticipation Under 35 U.S.C. §102: Weiner

Claims 14 is rejected as being anticipated by Weiner. Applicants respectfully traverse this rejection. This rejection relies on numerous reversible errors of fact and law, any one of which is fatal to the rejection.

The rejection at page 4 of the Office action states:

> Weiner et al. discloses the immunostimulatory oligonucleotide TCTCCCAGCGTGCGCCAT which comprises 2 CpG motifs (ODN 1758, Table 1, p. 10834). This immunostimulatory oligonucleotide comprises the formula, 5'……U3-U2-U1-X1-X2-Y-Z-X3-X4-D1-D2-D3…Dm-3' Wherein Y is a non-natural pyrimidine nucleoside (see 1st CG); Z is guanosine; Wherein X3, X4 and D1 are naturally occurring nucleosides (see TGC); Wherein D2 is an immunostimulatory moiety; wherein the immunostimulatory moiety is a 1', 2'-dideoxyribose (see Figure 3 of the instant specification, providing the structure of 1', 2'-dideoxyribose or a phosphorothioate linkage as shown in Figure 1 in the Stein and Cheng reference) and wherein at least one of X, U or D is an immunostimulatory moiety.

This mischaracterizes the teaching of Weiner in the following multiple ways:

(a) In ODN 1758 of Weiner, the underlined C is not a non-natural pyrimidine nucleoside; it is cytosine, a natural pyrimidine nucleoside. Note that the key word is "nucleoside", not "nucleotide". To the extent that the PTO is relying on the phosphorothioate linkage as rendering the underlined C "non-natural", it does not, since the term "nucleoside" does not include the phosphorous linkage.

(b) There is no 1', 2'-dideoxyribose in ODN1758 of Weiner. A 1', 2'-dideoxyribose has no base (it is replaced with a hydrogen), as shown in the instant application in Figure 3.

These are reversible errors of fact.

The Office Action further alleges that Weiner describes a control oligonucleotide that lacks unmethylated CpG motifs (ODN 1812) and lacks immunostimulatory activity and that "this" meets the definition of an immunostimulatory moiety. Apparently, "this" refers to the unmethylated Cs of ODN1758 as the immunostimulatory moiety. However, "this" would correspond to the Y position of the compound shown in claim 14, which in claim 14 is not an immunostimulatory moiety, but rather "a non-natural pyrimidine nucleoside".

In addition, claim 14 requires that when D2 is an immunostimulatory moiety, it is selected from the group consisting of 1'2'-dideoxyribose, C3-linker, Spacer 9, Spacer 18, 2-aminobutyl-1,3-propanediol linker, nucleoside methylphosphonate, and β-L-deoxynucleoside. Weiner does not teach any of these specific moieties at the D2 position. Thus, if the PTO is reading the phosphorothioate linkage at position D2 of Weiner as an immunostimulatory moiety, it is impermissibly reading out this limitation of claim 14.

These incorrect claim interpretations of claim 14 are reversible errors of law.

For these reasons, Applicants respectfully request that this rejection be with drawn.

Obviousness under 35 U.S.C. §103: Cook/Stein and Cheng

Claims 12 and 39 are rejected as being obvious over Cook and Stein and Cheng. Applicants respectfully traverse this rejection for the following reasons. First, as discussed above in reply to the anticipation rejection over Cook, Cook neither teaches nor suggests any of the specifically recited immunostimulatory moieties at any of their respectively recited specific positions. On this basis alone, Cook cannot render claim 12 or 29 obvious.

Second, the Office Action correctly notes that Cook does not disclose a specific sequence comprising a 4-thiouracil. However, the Office Action commits reversible error in its statement that "Cook describes generally incorporating modified bases including 4-thiouracil in the phosphorothioate oligonucleotides to increase their nuclease resistance in order to facilitate their use as therapeutic reagents (col. 7, lines 45+ and instant claim 39)." This mischaracterizes the teaching of Cook. At the cited section of Cook, that reference states that:

> To the extent that nucleoside-5'-O-(1-thiotriphosphate) analogs are substrates for suitable polymerases "phosphorothioateoligonucleotides" also include modified bases or modified sugars incorporated within the phosphorothioate nucleotide units of the oligonucleotides. Modified bases of the oligonucleotides of this invention include …" [a laundry list of possible bases, including 4-thiouracil].

Cook then goes on to add, at col. 8, lines 2-9:

> The oligonucleotides of the invention may also comprise modified nucleobases or nucleobases having **other** modifications consistent with the spirit of this invention, and in particular modifications that increase their nuclease resistance in order to facilitate their use as therapeutic, diagnostic or research reagents. (emphasis added)

Thus, Cook does not teach that 4-thiouracil increases nuclease resistance. This destroys the motivation alleged to be provided by Cook to make the claimed changes of claim 14.

Moreover, the Office action commits further error in its statement that "One of ordinary skill at the time the invention was made would have had a reasonable expectation of success given the underlying techniques are widely used and commonly known." (OA at page 6. Lines 18-20). To the contrary, one of ordinary skill in the art of immunostimulatory oligonucleotides, at the time the invention was made, believed that the CpG dinucleotide motif was essential to the immunostimulatory activity of such oligonucleotides and would have expected that changing the C of the essential CpG dinucleotide would abolish immunostimulatory activity. It is simply incorrect that the substitution of 4-thiouracil in the CpG dinucleotide was "widely used and commonly known." Only Applicants' own specification taught that at the time the invention was made.

For these reasons also, Applicants respectfully request that this rejection be withdrawn.

Obviousness under 35 U.S.C. §103: Weiner/Cook/Stein and Cheng

Claims 14 and 40 are rejected as being obvious over Weiner, Cook and Stein and Cheng. Applicants respectfully traverse this rejection. As demonstrated above, in Applicants' reply to the anticipation rejection over Weiner, Weiner does not teach or suggest any of the specifically recited immunostimulatory moieties at any of the respective specifically recited positions of claim 14. This alone should be dispositive of nonobviousness.

Moreover, as discussed above in Applicants' reply to the obviousness rejection over Cook, Cook does not teach that 4-thiouracil renders an oligonucleotide more resistant to nucleases. Finally, as discussed above, the substitution of 4-thiouracil for the C of the essential CpG dinucleotide was anything but "widely used and commonly known" in the field of immunostimulatory oligonucleotides at the time the invention of claims 14 and 40 was made.

For these reasons, Applicants respectfully request that this rejection be withdrawn.

Obviousness-type double patenting

Claims 12, 14, 39 and 40 are provisionally rejected for obviousness-type double patenting over various claims of co-pending applications 10/865,245 and 10/694,418. Because these applications are, respectively, later filed or of even filing date with the present application and have not been allowed, once all other presently maintained rejections are overcome, this application should be passed to allowance and any terminal disclaimers or other appropriate actions should be made in the cited applications. See MPEP 804.B.1.

Claims 12 and 14 are also rejected for obviousness-type double patenting over U.S. Patent No. 7,262,286. Claim 1 of this patent recites:

> An isolated immunostimulatory oligonucleotide compound, comprising an immunostimulatory dinucleotide of formula C*pG, wherein the immunostimulatory oligonucleotide compound is at least 6 nucleotides in length, and wherein C* is a cytidine analog selected from the group consisting of 5-hydroxycytosine, 5-hydroxymethylcytosine, N4-alkylcytosine and 4-thiouracil, G is guanosine, 2'-deoxyguanosine, or a guanosine analog, and p is an internucleotide linkage selected from the group consisting of phosphorothioate, and phosphorodithioate.

Claim 1 of this patent thus does not teach or suggest the positional modifications of claims 12 or 14. For purposes of obviousness-type double patenting, it is only what the claim of the recited reference teaches or suggests that is relevant, not what the specification teaches or suggests. Claims 1-4 of the cited patent do not include 1,2-dideoxyribose (where the base of the nucleoside is replaced by hydrogen) at all. Moreover, phosphorothioate is not one of the specific immunostimulatory moieties recited at any of the respective recited positions of claim 12 or 14.

Accordingly, Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner believes that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned attorney at 781-933-6630.

Respectfully submitted,

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